**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|
| IN RE APPLICATION OF | : Stefan Laufer *et al.* |
| SERIAL NO. | : 10/524,486 |
| FILED | : November 17, 2005 |
| FOR | : 2-Thio-substituted imidazole derivatives and their use in pahrmaceutics |

**DECLARATION UNDER 37 C.F.R. §1.132**

COMMISSIONER OF PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

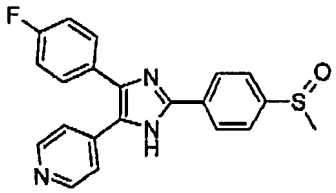
SIR:

Now comes Dr. Wolfgang Albrecht, co-inventor of the above identified invention, who deposes and states:

1. I am a graduate of Biotechnology, and received my doctorate degree from the Technical University in Berlin in the year 1990.
2. I have been working for Merckle since 1993. Since 2001, I have been leading the drug discovery programs at Merckle.
3. I have read and fully understood U.S. application, Ser. No. 11/321,631.
4. I have read and fully understood the Office Action of May 30, 2007 and the prior art cited therein.
5. The following experiments and investigations were carried out by me or under my direct supervision.

A number of compounds of the above identified application were prepared by the methods disclosed in said application and then subjected to the following test:

Microtiter plates were coated with the p38 MAP kinase substrate ATF-2 by incubating 50 µl of 20 µg/ml ATF-2 for one hour at 37°C. After the plates were washed three times with water, 50 µl of kinase mixture (= 50 mM Tris-HCl, 10 mM $MgCl_2$, 10 mM β-glycerol phosphate, 10 µg/ml BSA, 1 mM DTT, 100 µM ATP, 100 µM $Na_2VO_4$, 10 ng activated p38α) without and with increasing inhibitor concentrations were added into the wells and incubated for one hour at 37°C. The plates were washed three times with water and incubated with an anti-phospho-ATF-2 antibody for one hour at 37°. Thereafter, the plates were again washed three times with water and incubated with a goat alkaline phosphatase-labeled anti-rabbit IgG for one hour at 37°C. The plates were washed and incubated with 100 µl of a solution containing the phosphatase substrate 4-nitrophenolphosphate (3 mM 4-NPP, 50 mM $NaHCO_3$, 50 mM $MgCl_2$) for 1.5 hours at 37°C. Formation of 4-nitrophenolate was measured at 405 nm using a microtiter plate reader. Based on the inhibitor-concentration/response curves, $IC_{50}$-values were determined. For comparative purposes, $IC_{50}$ values of the Laufer *et al.* reference (US 6,432,988) were determined as well. Further, the $IC_{50}$ value of the known compound SB 203580 of the formula




was determined. Then, the ratio of the $IC_{50}$ value of compound SB 203580 to the $IC_{50}$ value of the tested compounds was calculated and presented in the attached table as

SB/test. This ratio allows the direct comparability of all data. The higher the ratio, the more active is the tested compound.

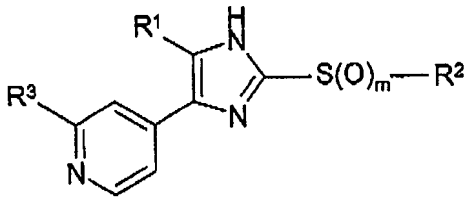
As can be seen, the compounds of the present application are surprisingly more active as compared to the compounds of Laufer *et al.* and as compared to compound no. 24 which is compound 1 of Wagner *et al.* (J. Org. Chem. **2003**, 68, 4527-4530).

6. The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

7. Further deponent saith not.

[Ort], Germany, [Datum] (Wolfgang Albrecht)

Annex: Table 1




| Compounds of the invention | $R^1$ | $R^2$ | $R^3$ | m | P38 SB/Test |
|---|---|---|---|---|---|
| 1 | 4-F-Ph | $CH_3$ | NH Ac | 0 | 4,46 |
| 2 | 4-F-Ph | $CH_3$ | $NHCOCH_2CH(CH_3)_2$ | 0 | 2.55 |
| 3 | 4-F-Ph | $CH_3$ | $NHCOCH_2CH_2Ph$ | 0 | 2.39 |
| 4 | 4-F-Ph | $CH_3$ | $NHCOCH_2CH_2Ph$ | 1 | 1.88 |
| 5 | 4-F-Ph | $CH_3$ | NHchex | 0 | 2.70 |
| 6 | 2,4-di-F-Ph | $CH_3$ | NHchex | 0 | 7.46 |
| 7 | 2,4-di-F-Ph | $CH_3$ | NHchex | 1 | 5.46 |
| 8 | 2,4-di-F-Ph | $CH_2CH_3$ | NHchex | 0 | 7.25 |
| 9 | 4-F-Ph | $CH_3$ | NH-2-$CH_3$-chex | 0 | 5.14 |
| 10 | 4-F-Ph | $CH_3$ | NH-Ph-3-F | 0 | 1.60 |
| 11 | 4-F-Ph | $CH_3$ | NH-Ph-3-$OCH_3$ | 0 | 1.71 |
| 12 | 4-F-Ph | $CH_3$ | NH-Ph-4-F | 0 | 1.07 |
| 13 | 4-F-Ph | $CH_3$ | NH-Ph-4-$OCH_3$ | | 2.06 |
| 14 | 4-F-Ph | $CH_3$ | $NHCH(CH_3)CH(CH_3)_2$ | 0 | 4.73 |
| 15 | 4-F-Ph | $CH_3$ | $NHCH(CH_3)CH(CH_3)_2$ | 1 | 5.50 |
| 16 | 4-F-Ph | $CH_3$ | NH-indan-1-yl | 0 | 2.02 |
| 17 | 4-F-Ph | $CH_3$ | NH-tetrahydronaphthyl | 0 | 2.19 |
| 18 | 4-F-Ph | $CH_3$ | NH-tetrahydropyran-4-yl | 0 | 16.15 |
| 19 | 4-F-Ph | $CH_3$ | NH-tetrahydropyran-4-yl | 2 | 13.00 |
| 20 | 4-F-Ph | $CH_3$ | $NH-CH(CH_3)CH(CH_3)_2$ S-enantiomer | 1 | 3.01 |
| 21 | 4-F-Ph | $CH_3$ | $NHCH_2$-cprop | 0 | 1.68 |
| 22 | 4-F-Ph | $CH_3$ | $NH-CH(CH_3)_2$ | 0 | 10.75 |
| 23 | 4-F-Ph | $CH_3$ | $NH-CH(CH_3)_2$ | 1 | 8.97 |
| 24 | 4-F-Ph | $CH_3$ | $NH-CH(CH_3)_2Ph$ | 0 | 1.40 |
| 25 | 4-F-Ph | $CH_3$ | NH-Ph | 1 | 4.88 |
| 26 | 4-F-Ph | $CH_3$ | $NH-CH_2CH_2$-thiophen | 0 | 2.18 |
| 27 | 4-F-Ph | $CH_3$ | $NH-CH(CH_3)CH_2CH_2Ph$ | 0 | 3.00 |
| 28 | 4-F-Ph | $CH_3$ | $NH-CH_2$-tetrahydrofuranyl | 0 | 1.41 |
| 29 | 4-F-Ph | $CH_3$ | $NH-(CH_2)_2OCH_3$ | 0 | 2.72 |
| 30 | 4-F-Ph | $CH_3$ | $NH-(CH_2)_3OH$ | 0 | 0.75 |
| Comparative compounds of US 6,432,988 (Laufer *et al.*) | $R^1$ | $R^2$ | $R^3$ | m | P38 SB/Test |
| | 4-F-Ph | $CH_2$-Ph-4-$SOCH_3$ | F | 0 | 0.02 |
| | 4-F-Ph | $CH_2$-Ph-4-$SOCH_3$ | H | 0 | 0.09 |
| chex = cyclohexyl; Ac = acetyl; cprop = cyclopropyl | | | | | |